REMARKS

Entry of the foregoing amendments, reconsideration or reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, and in light of the remarks which follow, are respectfully requested. By the present amendments, the claims have been amended such that they are no longer embrace treatment of multiple sclerosis or EAE. This amendment is made as the subject matter is covered by an earlier U.S. Patent. Such amendment is consistent with Applicant's understanding of allowable subject matter based on a recent interview with Examiner Gambel.

At the outset, Examiner was respectfully thanked for the recent personal interview with the undersigned and the inventor, Dr. Randolph J. Noelle. Therein, all of the outstanding rejections were discussed in detail. In particular, the 112 scope of enablement rejection was discussed at length. Particularly, the inventor discussed recent experimental evidence, as well as evidence submitted during prosecution of the patented application, which convincingly demonstrates that the administration of a CD40 ligand antagonist and particularly an antibody specific to CD40 ligand may be used to treat or prevent T-cell mediated autoimmune diseases. The discussed experimental data involved several different T-cell mediated autoimmune diseases, particularly in several accepted animal models for multiple sclerosis, as well as several accepted animal models for inflammatory bowel disease, chronic intestinal inflammation, type 1 diabetes and oophoritis. The Examiner indicated during the interview, that if this experimental evidence were formally submitted, that he would vacate the outstanding 112 scope of enablement rejection.

Moreover, the obviousness type double patent rejection was also discussed. Particularly, Applicant argued that it could not have been reasonably predicted based on the claims contained in this subject application, that the method could be used to treat multiple sclerosis, especially given the Examiner's acknowledgement as to the inherent unpredictabilities and complexities associated with treating this particular T-cell autoimmune disease. Indeed, the Examiner acknowledged that he himself typically does not allow claims directed to treatment to multiple sclerosis, absent convincing experimental evidence given the unique complexity and problems associated with designing and identifying methods and materials for effective treatment of this disease.

During the interview, the Examiner did not indicate whether he would be prepared to vacate the double patenting rejection. In particular, he noted that he would need to take this issue up with his supervisor and later advise whether the double patent rejection would be maintained. However, the day after the interview, Examiner Gambel contacted the undersigned, and advised that if the claims were amended to positively recite treating a T-cell mediated autoimmune disease other than multiple sclerosis that he would vacate the double patent rejection. As the Examiner's suggestion has been adopted, it is believed that the double patenting rejection should now be moot.

Turning now to the Office Action, Applicant note that the various objections to the disclosure. These objections are believed to have been overcome by the present amendments. In particular, new abstract entitlement are submitted which are believed to be appropriately descriptive of the claimed invention. Moreover, the specification has been amended to update the status of U.S Serial No. 08/481,735, particularly to recite that this is now U.S.

Patent 5,833,987. Based on the foregoing, withdrawal of the outstanding objections is respectfully requested.

Claims 1, 2 and 4-10 stand rejected under 35 U.S.C. 112, first paragraph as asserted not being adequately described or enabled by the teaching of the subject application. It is anticipated that this rejection will be overcome upon consideration of the experimental information attached to this reply, which was discussed at the recent interview with Examiner Gambel and the inventor, Dr. Noelle.

In the Office Action, the Examiner cites various references in support of his position that the treatment of autoimmune diseases is typically unpredictable. Also, the Examiner cites references to allegedly support that there is insufficient evidence to demonstrate a correlation between inhibiting the interaction between CD40 ligand and CD40 as a means of effective therapy of T-cell diseases in general. In further support of this rejection, the Examiner indicates that the claimed antagonist encompass a myriad of different molecules including antibodies, proteins, non-protein molecules which may behave differently.

At the outset, it is anticipated that this rejection should be moot based upon consideration of the experimental evidence, and particularly in light of the present amendments. With respect to the alleged myriad of different gp39 antagonists, Applicant notes that Claim 1 has been amended to recite that the gp39 antagonist is selected from the group consisting of antibodies specific to CD40 ligand and antibody fragment specific to the CD40 ligand, soluble CD40, and soluble CD40 fusion proteins. Therefore, the claims no longer embrace a myriad of different CD40 ligand antagonists. However, Applicant

respectfully submits that the scope of the claims was appropriate even absent the amendment given the seminal and pioneering nature of Applicant's discovery.

With respect to the efficacy of the claimed methods which are directed to the treatment of T-cell mediated autoimmune diseases generically, Applicant respectfully submits that it is been convincingly shown in a number of accepted animal models, that the administration of a gp39 antagonist, for example, an antibody specific to CD40 ligand provides an effective method for treatment or prophylaxsis of a variety of different T-cell autoimmune diseases. Indeed, this has been demonstrated in several accepted animal models for multiple sclerosis, *i.e.*, several EAE models, as well as in several animal models for inflammatory bowel disease, and chronic intestinal inflammation. Also, the fact CD40 ligand and CD40 interactions are essential for initiation of insulitis and diabetes is demonstrated by recent experimental evidence which is evidenced *e.g.*, by an article by Balsa et al Journal of Immunology, Vol. 159, pages 4620-4627 (1997). Still further, Applicant note that the role of CD40 and CD40 ligand interactions in the pathology of oophoritis has also been shown.

Particularly, Applicant refers to the data submitting during prosecution of the earlier applicant relating to EAE. Applicant submitted, during prosecution of the parent application, now issued, data in the chronic EAE model as well as the relapse model, which demonstrated that administration of an antibody to CD40 ligand provided an effective means for intervening in the disease process. Also, Applicant attachs to this reply an article by Howard et al. [Journal in *Clinical Investigation*, Vol 103, No. 2 (January 1999) pp. 281-290] which shows that the administration of anti-CD40 ligand antibody in a relapsing EAE animal model severely inhibited disease induction, myelin peptide-specific delayed-type hypersensitivity

responses, and the induction of encephalitogenic, effector cells, as well as impairing the expression of clinical disease in recipients of encephalitogenic T-cells. In fact, data suggests that CD40-CD40 ligand interactions are involved in directing the CNS migration of such cells, and that the blockade of CD40 ligand – CD40 interactions has application in an immunotherapeutic strategy for treating ongoing T-cell mediated autoimmune diseases.

Also, Applicant further attachs to this Reply information from a grant by the inventor, which presents yet additional data in another EAE model. In particular, the Examiner is respectfully referred to the preliminary studies referred to at pages 18 and 19, which discuss that the administration of anti-CD40 ligand inhibited the onset of PLP-EAE in SJL/j. mice, and that treatment at the disease onset causes a significant decrease of clinical symptoms compared to control mice, and that even after encephalitogenic T-cells are present, that the administration of antibody to CD40 ligand can interfere with the effector phase of the disease.

Also, at page 19, the inventor discusses the basis for the therapeutic effect of anti-CD40 ligand during priming. Specifically, he explained that, during the priming phase of EAE, their results are consistent with the fact that anti-CD40 ligand prevents the differentiation of T-cells to an inflammatory *in vivo* type, which blocks IL-2 production. Also, the data obtained further suggests that treatment with antibody to CD40 ligand inhibits disease onset, by changing the effector properties of MOG-reactive T-cells, and that anti-CD40 ligand therapy inhibits Th_1 development and the ability of T-cells to cross the blood brain barrier. Still further, it is discussed therein that treatment with an antibody to CD40 ligand in animals with established EAE resulted in a reduction of clinical symptoms.

Additionally, Applicant further attaches to this Reply, for the Examiner's review, a brief overview of phase I clinical results obtained in a human MS clinical trial being conducted at Dartmouth. It should be noted that all patients in the study have demonstrated stabilization or improvement of their EDSS scores. This is believed to provide further support of the efficacy of the claimed method.

Also, the Applicant respectfully refers the Examiner to information attached hereto relating to the treatment or intervention inflammatory bowel disease or chronic experimental colitis. Specifically, the Examiners is referred to the article entitled "Chronic and Experimental Colitis is Dependent on the CD154/CD40 Pathway and Can be Intervened by Anti-CD154 Administration". This reference contains experimental data substantiating treatment of mice in an accepted animal model of IBD with anti-CD40L antibody substantially impaired disease progression.

Further, Applicant respectfully refer to Liu et al., *Journal of Immunology*, Vol. 163 (1999) pp. 4049-4057, which studies the hyper expression of CD40 ligand in inflammatory bowel disease, and teaches that it contributes to pathogenic cytokine production. It should be noted that the authors conclude based on their findings, that CD40 ligand regulation is involved in pathogenic cytokine production which is significant to inflammatory bowel disease, and that blockade of CD40-CD40 ligand interaction may have therapeutic benefits for treating such patients.

Further, the article contains information which shows that the addition of a blocking monoclonal antibody to specific to CD40 ligand or CD40 in cultures comprising freshly isolated lamina propria T-cells obtained from patients with inflammatory bowel disease

significantly decreased monocyte IL-2 and TNF production, both of which cytokines are involved in the disease process.

Still further, Stuberg et al., *Journal of Experimental Medicine*, Vol. 183 (1996) pp. 693-698, similarly describes that blocking of the CD40 ligand-CD40 interactions in yet another experimental model for a Th_1 mediated disease, *i.e.*, inflammatory colitis, particularly during the induction phase of the Th_1 response, prevented cytokine production by lamina propria CD40 positive T-cells.

Also, in further support of the general efficacy of the invention, Applicant respectfully refers to yet another article [Blosa et al., *Journal of Immunology*, Vol. 159 (1997) pp. 4620-4627] which discloses that CD40 ligand/CD40 interactions are necessary for the initiation of insulitis and diabetes in NOD mice, which comprise an accepted animal model for type 1 diabetes. This article shows that the administration of an antibody to CD40 ligand prevented insulitis by inhibiting the development and further accumulation of pathogenic Th_1 cells. While the subject claims are directed to treatment, not prevention of T-cell autoimmune diseases, the inventor noted during the recent interview that the methods and reagents suitable for intervening early in type 1 diabetes, are being developed. In particular, this is evidenced by an article by Flanders et al., *Autoimmunity*, Vol. 29, No. 3 (1999) pp. 235-246, also attached to this Reply, which describes that an alternative approach to prevention of type 1 diabetes may include a vaccine in early childhood to induce tolerance to critical auto antigens. Also, this reference reviews the status of current diabetes prevention trials in humans and reports that new intervention strategies are being currently tested in animal models. Based on this information, and the Stuberg et al. article, it is reasonable to conclude

that administration of an antibody to CD40 ligand as well as other gp39 antagonists will provide an effective means for intervening in type 1 diabetes, particularly early on in the disease process.

Finally, the inventor also referred to recent experimental data in an animal model for oophoritis, which shows that the administration of antibodies to CD40 ligand (MR-1) blocks the transfer. Specifically, Applicant further attaches to this Reply data which shows that MR-1 administration blocked the transfer of disease by T-cells for D3TX mice, and that MR-1 inhibited the disease and autoimmunity in D3TX mice. This data is also attached to Applicant's Reply. Based on the foregoing, and as agreed by the Examiner at the recent interview, withdrawal of the outstanding 112 scope of enablement rejections is respectfully requested.

Also, claim 9 was rejected under 35 U.S.C. 112, second paragraph is being indefinite. This rejection should be moot, as the claim has been amended to clarify that a chimeric antibody is an antibody containing constant regions and variable regions from different species antibodies.

Also, claims 1 and 2 were rejected under 35 U.S.C. 102(e) as essentially being anticipated by Cobbold et al. This rejection should be moot in view of the present amendments.

Finally, claims 1 and 4-10 stands rejected under the judicially created doctrine of obviousness-type double patenting as assertively being unpatentable over claims 1and 2 of U.S. Patent 5,833,947. This rejection should be moot, as Applicant has amended claim 1 to positively recite that the T-cell mediated autoimmune disease is not multiple sclerosis. The

Examiner indicated, after the interview, based on a discussion with his supervisory Examiner, that such amendment would overcome the double patenting rejection. In particular, he acknowledged that it could not have been reasonably predicted based on the subject claims which are directed to treating a T-cell mediated autoimmune disease other than multiple sclerosis that the administration of an antibody to CD40 ligand or another CD40 ligand antagonist would provide an effective treatment for multiple sclerosis, given the unique problems and unpredictabilities associated with treating this disease.

Based on the foregoing, it is anticipated that this application should be in condition for allowance. A notice to that effect is respectfully solicited. However, if any issues remain outstanding after consideration of this reply the Examiner respectfully requested to contact the undersigned that prosecution may be expedited.

Respectfully submitted,

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